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(71) Applicant *(for all designated States except US)*: **ISIS PHARMACEUTICALS, INC.** [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BHAT, Balkrishen** [IN/US]; 911 Rosemary Avenue, Carlsbad, CA 92009 (US). **SWAYZE, Eric** [US/US]; 7789 Palenque Street, Carlsbad, CA 92009 (US). **PRAKASH, Thazha, P.** [IN/US]; 6928 Pear Tree Drive, Carlsbad, CA 92009 (US). **ALLERSON, Charles** [US/US]; 971 Beach Crest Court, Carlsbad, CA 92009 (US). **DANDE, Prasad** [IN/US]; 348 Pine Avenue, Apartment 13, Carlsbad, CA 92008 (US). **GRIFFEY, Richard, H.** [US/US]; 360 Barsby Street, Vista, CA 92084 (US).

(74) Agent: **CALDWELL, John**; Woodcock Washburn LLP, 2929 Arch Street - Suite 1200, Philadelphia, PA 19104-2891 (US).

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26 June 2008

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(54) Title: POSITIONALLY MODIFIED siRNA CONSTRUCTS

(57) Abstract: The present invention provides oligomeric compounds having sufficient complementarity to hybridize to a nucleic acid target and methods for their use in modulating gene expression. In one embodiment the oligomeric compounds comprise double stranded constructs wherein one of the strands capable of hybridizing to a nucleic acid target, and has a plurality of modified ribofuranosyl nucleosides at defined locations. The presense of modifications at such defined positions greatly enhances the properties of the corresponding compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/17485

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07H 21/04**(2006.01)

USPC: 536/24.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST: sirna, modified nucleotides, 4' thio, 2'-Omethyl, phosphorothioate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0143732 (FOSNAUGH et al.) 31 July 2003 (31.07.2003), see entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Tracy Vivlemore

Telephone No. 571-272-1600

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/17485

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-22

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-22, drawn to a composition of a double stranded oligonucleotide comprising 3-8 modifications at positions 1, 2, 3, 9, 12, 17, 18 or 19 of the first (antisense) strand.

Group 2, claim(s) 23-37, drawn to a composition of a double stranded oligonucleotide comprising one of three patterns of modification on the first (antisense) strand.

Group 3, claim(s) 38-59, drawn to a composition of a double stranded oligonucleotide comprising 3-7 modifications at positions 5, 6, 9, 10, 17, 18 or 19 on the first (antisense) strand.

Group 4, claim(s) 60-80, drawn to a composition of a double stranded oligonucleotide comprising 3-6 modifications at positions 5, 11, 14, 17, 18 or 19 on the first (antisense) strand.

Group 5, claim(s) 81-92, drawn to a composition of a double stranded oligonucleotide comprising 3-7 modifications at positions 5, 8, 11, 14, 17, 18 or 19 on the first (antisense) strand.

Group 6, claim(s) 93-111, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 3, 7 or 15 on the first (antisense) strand.

Group 7, claim(s) 112-130, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 4, 10 or 19 on the first (antisense) strand.

Group 8, claim(s) 131-148 and 511, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 4, 8 or 16 on the first (antisense) strand.

Group 9, claim(s) 149-167, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 4, 11 or 19 on the first (antisense) strand.

Group 10, claim(s) 168-186, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 3, 10 or 18 on the first (antisense) strand.

Group 11, claim(s) 187-206, drawn to a composition of a double stranded oligonucleotide comprising 3-7 modifications at positions 6, 7, 10, 11, 17, 18 or 19 on the first (antisense) strand.

Group 12, claim(s) 207-223, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 4, 9 or 18 on the first (antisense) strand.

Group 13, claim(s) 224-242, drawn to a composition of a double stranded oligonucleotide comprising 3-6 modifications at positions 3, 9, 12, 17, 18 or 19 on the first (antisense) strand.

Group 14, claim(s) 243-260, drawn to a composition of a double stranded oligonucleotide comprising 3-5 modifications at positions 15, 16, 17, 18 or 19 on the first (antisense) strand.

Group 15, claim(s) 261-280, drawn to a composition of a double stranded oligonucleotide comprising 3-4 modifications at positions 5, 8, 11 or 14 on the first (antisense) strand.

Group 16, claim(s) 281-300, drawn to a composition of a double stranded oligonucleotide comprising 3-5 modifications at positions 1, 2, 3, 9 or 12 on the first (antisense) strand.

Group 17, claim(s) 301-319, drawn to a composition of a double stranded oligonucleotide comprising 3-6 modifications at positions 6, 12, 16, 18, 19 or 20 on the first (antisense) strand.

Group 18, claim(s) 320-339, drawn to a composition of a double stranded oligonucleotide comprising 3-7 modifications at positions 6, 7, 10, 11, 18, 19 or 20 on the first (antisense) strand.

Group 19, claim(s) 340-357, drawn to a composition of a double stranded oligonucleotide comprising modifications at positions 6-8 or positions 9-11 on the first (antisense) strand.

Group 20, claim(s) 358-374, drawn to a composition of a double stranded oligonucleotide comprising 2-3 modifications at positions 4, 10 or 19 on the first (antisense) strand.

Group 21, claim(s) 375-394, drawn to a composition of a double stranded oligonucleotide comprising 3-6 modifications at positions 3, 4, 10, 11, 17 or 18 on the first (antisense) strand.

Group 22, claim(s) 395-414, drawn to a composition of a double stranded oligonucleotide comprising 6-10 modifications at positions 1, 2, 3, 6, 9, 12, 15, 18, 19 or 20 on the first (antisense) strand.

Group 23, claim(s) 415-432, drawn to a composition of a double stranded oligonucleotide comprising 3-7 modifications at positions 9-11 or positions 18, 19 or 10 on the first (antisense) strand.

Group 24, claim(s) 433-451, drawn to a composition of a double stranded oligonucleotide comprising 2-4 modifications at positions 16, 18, 19 or 20 on the first (antisense) strand.

Group 25, claim(s) 452-471, drawn to a composition of a double stranded oligonucleotide comprising modifications at positions 1-3 or positions 7-9 or positions 12-14 or positions 13-15 on the first (antisense) strand.

Group 26, claim(s) 472-489, drawn to a composition of a double stranded oligonucleotide comprising modifications at positions 1-3 or positions 3-5 on the first (antisense) strand.

Group 27, claim(s) 490-510, drawn to a composition of a double stranded oligonucleotide comprising modifications at positions 6-8, or positions 9-11 or positions 12-14 or positions 15-17 or positions 18-20 on the first (antisense) strand.

The inventions listed as Groups 1-27 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of groups 1-27 is a double stranded oligonucleotide composition comprising particular modification patterns on the antisense strand. The particular modification patterns do not make a contribution over the prior art, as shown in the reference of McSwiggen (US 2003/0170891), who teaches at pages 6-7 siRNA compositions comprising 1-10 modified nucleotides. While McSwiggen does not explicitly teach the specific patterns claimed, those in the art would recognize that production of a particular modification pattern is a matter of design choice and routine optimization and therefore the claimed inventions lack inventive step over the teachings of McSwiggen.